Remarks

Applicants thank Examiners Mary M. Schmidt and Sean McGarry for the personal interview on March 12, 2003. During the interview, Applicants' representatives, Aaron Schwartz and John Covert, explained the claimed invention and how the organic cationic precursor molecules of the claimed transfection particles differ from prior art detergents or lipids. Applicants' representatives also discussed the amendment herein presented to claim 1, which is made to further clarify the claimed transfection particles. Applicants' representatives also traversed the Examiner's enablement rejection under 35 U.S.C. § 112 by reiterating arguments made in previous replies.

Reconsideration of this Application is respectfully requested. Admission of the above claim amendments or additions is respectfully requested for purposes of presenting rejected claims in better form for consideration on appeal. Upon entry of the foregoing amendment, claims 1, 2, 5-7, 8-33, 37-41, 45, 46, 48 and 49 are pending in the application, with claims 1, 48 and 49 being the independent claims. Claims 3, 4, 42 and 43 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. These claims are sought to be cancelled solely to expedite prosecution of the remaining, pending claims. Claims 42 and 43 were meant to be cancelled in the previous Reply filed on August 27, 2002, but were inadvertently omitted from the amendment requesting claim cancellations on page 2. *See* PTO File Wrapper Paper No. 17, Amendment and Reply Under 37 C.F.R. § 1.111, page 2, line 5; page 13, lines 10-13; and page 22, line 2. Claims 1, 5 and 6 are sought to be amended. Support for the amendments to claim 1 may be found in original claims 3 and 4. Claims 5 and 6 have been amended only to change their

dependencies. New claim 49 is sought to be added. Support for claim 49 can be found in original claim 8. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Applicants' Invention

Applicants' claimed transfection particles are formed by associating organic cationic precursor molecules with DNA. Each precursor molecules is composed of four parts: i) at least one functional group for binding to one or more other detergent molecules; ii) at least one lipophilic residue, iii) a non-toxic recipient backbone, and iv) a cationic group (also referred to as a "headgroup") for binding to nucleic acid molecules. The positively charged headgroups of these precursor molecules associate with the negatively charged phosphate groups on the DNA. Next, the precursor molecules assembled about the DNA dimerize or oligomerize thereby condensing the DNA and forming the claimed transfection particles. Depending on the functional group for binding to one or more other detergent molecules, linkage may occur spontaneously upon contact of the precursor molecules when bound to DNA. *See* Written Description, p. 27, first full paragraph. Alternatively, linkage may need to be mediated by an additional agent, such as oxygen. The process of forming Applicants' transfection particles is described in the Written Description from the fifth full paragraph on page 26 through the second full paragraph on page 28.

Rejections under 35 U.S.C. § 112

The Examiner has maintained the rejection of claims 1-33, 37-43, 45-46 and 48 under 35 U.S.C. §112 , first paragraph, on grounds that the specification "does not reasonably provide enablement for the scope of compositions claimed . . ., nor methods of making and using said compositions in cells in any whole organism such as humans for therapeutic purposes." See PTO File Wrapper Paper No. 18, p. 2, second full paragraph. Applicants respectfully traverse the rejection.

Applicants understand this enablement rejection to have two components. One component pertains to whether the description enables any use of the claimed compositions. Applicants respectfully traverse this aspect of the rejection. The legal standard for enablement as it relates to composition claims can be found in the M.P.E.P.:

> . . . when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use. If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention.

M.P.E.P. (Eighth) §2164.01(c) How to Use the Claimed Invention (2001). Thus, the Examiner must provide an explanation, supported by evidence, as to why the specification fails to enable every described use.

Applicants' compositions can be used for *in vitro* transfection which is a notoriously well known use. This use is demonstrated in the working examples provided in the Written Description from pages 37-79. Moreover, the Examiner has acknowledged this use: ". . . it is agreed that the method of transfecting cells in cell culture is not a serious burden on one of skill in the art. Although the exact concentration of liposomes must be determined

so that the transfection is not toxic, such assays are easily performed by use of concentration gradients in the laboratory." *See* PTO File Wrapper Paper No. 14, page 17, lines 9-12. (See also *Id.* at page 19, lines 18-19: ". . . it is not disputed that liposomes are well-known for in vitro transfection."). Because Applicants have demonstrated and the Examiner has acknowledged that the claimed compositions are enabled for at least one use (here, *in vitro* transfection), it is irrelevant whether or not Applicants have enabled *other* uses of the claimed compositions. Hence, any argument or evidence related to the predictability or unpredictability of *in vivo* therapeutic use of the claimed compositions is irrelevant since the examiner agrees that in vitro transfection is enabled. Thus, Applicants respectfully request the Examiner to withdraw this aspect of the enablement rejection under 35 U.S.C. § 112, first paragraph.

The remaining component of the Examiner's enablement rejection is directed to the scope of the claimed compositions. The Examiner relies upon references which allegedly disclose the unpredictability of making liposomal structures which encapsulate DNA for transfecting cells. *See* PTO File Wrapper Paper No. 18, pp. 8-12. These references include Zelphati *et al.*, Staatz *et al.*, Schott *et al.*, and Freeman *et al.* and have been cited in previous office actions. *Id.* However, because Applicants are not claiming a liposomal composition, any alleged unpredictability in the making of liposomal structures is irrelevant to the enablement inquiry. Applicants respectfully traverse this aspect of the rejection and reiterate that the Examiner has not met her burden of demonstrating that the specification fails to enable how to make the full scope of the claimed inventions.

According to Zelphati *et al.*, a DNA liposome is made by mixing DNA with cationic lipids, wherein the lipids contain a positively charged headgroup, and two long lipophilic

carbon chains. *See* Zelphati *et al.*, p. 33, bottom half. The positively charged head groups associate with the negatively charged DNA phosphate backbone. *Id.* In a liposome, the lipophilic chains form a lipid bi-layer. The net result is a lipid bi-layer sphere which encapsulates DNA. *See* Zelphati *et al.*, p. 40, fig. 1.

In contrast, Applicants' claimed transfection particles are made by an entirely different process. Moreover, Applicants nowhere assert that a liposome structure is required for the particles to be effective. Applicants' Written Description describes the process of making the claimed transfection particles from the fifth full paragraph on page 26 through the second full paragraph on page 28. First, the DNA is associated with organic cationic precursor molecules. The positively charged headgroups of these precursor molecules associate with the negatively charged phosphate groups on the DNA. However, rather than forming liposomes, the precursor molecules assembled about the DNA dimerize or oligomerize thereby condensing the DNA and forming the claimed transfection particles. Depending on the reactive groups available for dimerization or oligomerization, linkage may occur spontaneously upon contact of the precursor molecules when bound to DNA. *See* Written Description, p. 27, first full paragraph. Alternatively, linkage may need to be mediated by an additional agent, such as oxygen. Hence, unpredictability in liposomal formation is not relevant to the predictability of formation of Applicants' claimed transfection particles.

The Examiner has also relied upon post-file date references, co-authored by one or more of the inventors, as evidence allegedly of the unpredictability of forming Applicants' claimed transfection particles. In particular, the Examiner apparently relies upon Dauty *et al.*, *J. Am. Chem. Soc. 123*:9227-9234 (2001) (Dauty *et al.*) to assert that choice of

head group for the organic cationic precursor molecule is a factor that leads to unpredictable and variable results in transfection particle formation. PTO File Wrapper Paper No. 18, p. 16, lines 5-11; and p. 18, lines 2-8. Applicants respectfully assert that the Examiner has misconstrued the reference and drawn an incorrect conclusion.

Applicants wish to point out that "thiol amphiphiles" and "headgroups" are not the same thing. "Headgroups," referred to in Dauty *et al.*, carry a positive charge and associate with the negatively charged DNA phosphate backbone. *See* Dauty *et al.*, Abstract, third sentence, and p. 9229, Table 1. Dauty *et al.* refers to "thiol amphiphiles" which are merely one type of organic cationic precursor molecules having a thiol group (for binding to one or more other cationic precursor molecules), a lipophilic residue, a nontoxic backbone, and some head group. The term "amphiphile" refers to a molecule which has a polar head group (e.g., positively charged amine) that is hydrophilic and a residue (e.g., a long carbon chain) which is lipophilic. Table 1 of Dauty *et al.* shows four different thiol amphiphiles, with two different head groups. C_{12}COrn, C_{14}COrn and C_{16}COrn each have an ornithyl head group (with two positively charged amines), and C_{14}CSper has a spermine head group (with four positively charged amines). It is very important to note that all of these thiol amphiphiles with different head groups resulted in transfection of DNA. *See* Dauty *et al.*, Table 1, far right column. Hence, any allegation that "thiol amphiphiles" are the only "headgroups" shown to form transfection particles is misleading and inaccurate.

Moreover, the oligoamines or oligolysines referred to by Dauty *et al.* are not encompassed by Applicants' organic cationic precursor molecules. Dauty *et al.* generally refers to two types of compounds for "freezing" DNA particles:

> We recently described a general method for "freezing" such small DNA particles. It makes use of polymerizable α,ω-bisthiol oligocations ***or***

> of dimerizable cationic thiol detergents for DNA condensation (Figure 1). Subsequent oxidation to disulfides converts the reversible condensing agent into a polymer or a lipid, ***respectively***.

See Dauty *et al.*, p. 9228, left column, second full paragraph (emphasis added). The α,ω-bisthiol oligocations (having two SH groups) are shown in Figure 1 of Dauty *et al.* and are clearly different from the dimerizable cationic thiol detergents also shown in Figure 1. In contrast to the α,ω-bisthiol oligocations, the cationic thiol detergents have a lipophillic residue, which is also required by Applicants' claim 1 (thrice amended) and claim 49 (new). The sentence which follows the above quoted passage[1] is descriptive only of α,ω-bisthiol oligocations, and should not be construed as referring to cationic thiol detergents. In contrast, the second and third sentences following the above passage[2] do refer to cationic thiol detergents and provide further evidence that Applicants' claims are enabled. Moreover, C_{12}COrn and C_{16}COrn, both shown in Table 1 of Dauty *et al.* as capable of transfecting cells, are described in the application at, for example, figure 14 and examples 4 and 20, and constitute further evidence that Dauty *et al.* enables Applicants' claims.

Applicants respectfully point out that although Dauty *et al.* focused on thiol amphiphiles, nowhere does this reference disclose or suggest that thiol amphiphiles are the only cationic precursor molecules capable of forming transfection particles. Also, nowhere does Dauty *et al.* disclose or suggest that transfection particles must be monomolecular with

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[1] "Stable particles formed with oligoamines or with oligolysines were eventually small but not monomolecular with respect to plasmid DNA." *See Id.*

[2] "Solutions of particles resulting from the DNA template-assisted dimerization of detergents into gemini surfactants, however, were remarkably homogenous. Laser light scattering and electron microscopy showed them to be made of individually condensed DNA molecules." *See Id.*

respect to the DNA in order to function. The statements and reported results in Dauty *et al.* do not contradict Applicants' Written Description such that one would conclude that Applicants' description does not enable the claimed scope of transfection particles formed from organic cationic precursor molecules.

Solely to expedite prosecution and not in acquiescence to the rejection, claim 1 has been amended to be directed to a transfection particle comprising one or more nucleic acid molecules condensed by organic cationic molecules, the particle being obtained by (1) condensing the one or more nucleic acid molecules with identical or different organic cationic precursor molecules without crosslinking any of the one or more nucleic acid molecules, and (2) thereafter obtaining cationic molecules by linking the precursor molecules to each other with one or more covalent bonds, wherein the one or more nucleic acid molecules remains condensed by the cationic molecules; wherein the cationic precursor molecules comprise: a) at least one functional group for binding to one or more other of the precursor molecules, wherein the functional group is a dimerizable or polymerizable functional group selected from the group consisting of thiols, acid hydrazides, aldehydes, amines, and ethylene residues that are suitably substituted to provide enamines upon reaction with an amine, b) at least one lipophilic residue, c) a non-toxic recipient backbone, and d) a cationic group for binding to nucleic acid molecules. The claim as amended provides clear structural and functional characteristics for each element of the claimed particles. Claim 49, an independent form of original claim 8, provides a clear structural description of a preferred subset of precursor molecules employed in the transfection particles. The full scope of each of these claims is enabled by the written description.

Applicants respectfully request the Examiner to reconsider and withdraw all rejections made under 35 U.S.C. § 112.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

In the Claims:

Claims 3, 4 , 42 and 43 have been cancelled.

Claim 1 has been amended as follows:

1. (thrice amended) A transfection particle comprising one or more nucleic acid molecules condensed by organic cationic molecules, said particle being obtained by (1) condensing said one or more nucleic acid molecules with identical or different organic cationic precursor molecules without crosslinking any of said one or more nucleic acid molecules, and (2) thereafter obtaining cationic molecules by linking the precursor molecules to each other with one or more covalent bonds, wherein [the linked precursor molecules remain condensed on] said one or more nucleic acid molecules remains condensed by said cationic molecules;
wherein the cationic precursor molecules comprise:

a) at least one functional group for binding to one or more other of said precursor molecules, wherein said functional group is a dimerizable or polymerizable functional group selected from the group consisting of thiols, acid hydrazides, aldehydes, amines, and ethylene residues that are suitably substituted to provide enamines upon reaction with an amine,

b) at least one lipophilic residue,

c) a non-toxic recipient backbone, and

d) a cationic group for binding to nucleic acid molecules.

Claim 5 has been amended as follows:

5. (twice amended) The transfection particle of claim [4] 1, wherein the lipophilic residue is selected from the group consisting of lipophilic amides, esters and ethers.

Claim 6 has been amended as follows:

6. (twice amended) The transfection particle of claim [3] 1, wherein the functional group for binding to nucleic acid molecules is selected from an amine or derivative thereof.

New claim 49 has been added.